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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,329	BONDAREV ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *3,5,18,20,30-35 and 41-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-17,19,21-29 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/4/06; 5/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 4/10/06 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/12/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 4/10/2006, claims 1-58 are pending in the application. Claims 3, 5, 18, 20, 30-35, and 41-58 remain withdrawn. Claims 1, 2, 4, 6-17, 19, 21-29, and 36-40 are currently under examination.

This application contains claims that are drawn to inventions nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claims 2, 17, 24, 26–28, and 37 remain objected to because the claims recite limitations to non-elected inventions such as an antisense sequence or an antisense compound, a construct capable of expressing human L1RT antisense sequence, an inorganic compound, and peptide. Claims 26–28 recite limitations of non-elected inventions. Appropriate correction is required.

Applicants have acknowledged the objection but have elected not to amend the claims at this time, stating that deletion or correction of the claims is unwarranted at this time.

Applicants are advised that generic claims 1 and 16 stand rejected as explained below.

New objections necessitated by Applicants' amendments to the claims:

Claims 2, 6, 17, and 21 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Applicants' amendments to claims 1 and 16 have narrowed the scope of claims 1 and 16 relative to claims 2 and 6, 17 and 21, which depend from claims 1 and 16, respectively. The Examiner notes that it is unclear whether or not Claims 1 and 16 are limited to AZT, ddI, and d4T, or whether claim 1 includes any nucleoside analog. As amended, claims 1 and 16 recite wherein the inhibitor or antagonist is a nucleoside analog 3'-azido-2',3'-dideoxythymidine (AZT),..." The inclusion of the recitation of "nucleoside analog" may be interpreted to mean that any nucleoside analog, including those specifically recited, may be used in the claimed method (see Written Description Rejection, below).

Claim 4 is objected to for being dependent on a withdrawn claim, claim 3.

Correction is required.

Response to Arguments—Claim Rejections - 35 USC § 112

Claim 28 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' amendment to Claim 28 is acknowledged. However, the claim remains indefinite because the claim recites "a protein comprising SEQ ID NO:1." A review of the sequence listing shows that SEQ ID NO:1 is a nucleic acid not a protein.

Clarification and/or correction is required.

As noted above, Claim 28 is drawn to a non-elected invention: L1RT antisense.

New rejection under 35 USC §112, second paragraph, necessitated by Applicants' amendments to the claims:

Claim 16 is rejected as being indefinite because the claim recites the limitation "the organic compound" in line 5. There is insufficient antecedent basis for this limitation in the claim.

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Claims 1, 2, 4, 6, 8, 9, 16, 17, 19, 21, 23, and 25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner notes that claim 8 was inadvertently omitted from the list of rejected claims under this section in the previous Office Action. However, the limitations of Claim 8 were addressed under this section in the previous Action. No new grounds of rejection are applied to claim 8.

As noted above, Applicants' amendment to claims 1 and 16 comprises the recitation "wherein the inhibitor or antagonist is a nucleoside analog..." in line 7. The recitation "nucleoside analog" encompasses any nucleoside analog, including those now recited in claim 1.

As explained in the previous Action, adequate written description does not exist in the instant application for all these methods. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of nucleoside analogs as now required to practice the genus of methods, as now claimed.

It appears that Applicants have attempted to narrow the scope of the instant claims to three specific nucleoside analogs, AZT, ddI, and d4T, which were found to be adequately supported by the specification. However, the inclusion of the broad term "nucleoside analog" in front of the list of specific nucleoside analogs creates the possibility that the claims may yet encompass methods for treating cancer using any nucleoside analog, for which adequate written description support does not exist.

Furthermore, claims 2, 6, 17, and 21 broaden the scope of the invention, albeit improperly, to include any organic compound, which, as the previous Action explained, do not have adequate written description support in the instant application.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not

predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

As explained in the previous Action, the prior art indicates a degree of unpredictability in the art as it relates to the use of nucleoside analogs to suppress telomere lengthening and cell growth in cultured cells. Different nucleoside analogs can have different specific effects.

Accordingly, only methods comprising the use of AZT, ddI, and d4T meet the written description requirement.

Removing the recitation "nucleoside analog" from claims 1 and 16, and amending claims 2, 6, 17, and 21 to properly limit the invention of claims 1 and 16, respectively, would overcome this rejection.

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Claims 1, 2, 4, 6-15, 39 and 40 remain rejected for lack of written description for reasons of record. Claims 1, 2, 4, and 6-9 are now rejected under this section in view of Applicants amendments to the claims.

The instant claims are drawn to methods for treating or preventing any cancer in a human, wherein the cancer is characterized by or is due to cells showing alternative lengthening of telomeres induced or mediated by L-1 (LINE-1) retrotransposon encoded reverse transcriptase (RT).

Applicants have not demonstrated that they are in possession of the genus of all such methods for treating any individual suffering from ALT-type cancers because Applicants have not described a representative number of cancers that are "due to" or "induced by" LINE-1 RT or set forth any guidance as to how to identify all such cancers.

It is unclear from present disclosure and the state of the art at the time of filing how the skilled artisan would be able to determine whether the nascence of particular cancer was due to or induced by LINE-1 RT.

As explained in the previous Action, the post-filing art recognizes that cancer is a multifactorial event, in which numerous alterations contribute to the emergence of the malignant cell (Bocchetta et al., 2004, *Oncogene* 23:6484-6491). Malignant tumor growth is a dynamic process in which it is difficult to identify a unique event that caused the process (Bocchetta et al.).

The question is how does one determine that a particular cancer was induced by LINE-1 RT? Therefore, which cancers are treatable by the methods of the instant claims?

The specification teaches (page 2) that up to 30% of human tumors of different types do not express telomerase, and that the presence of alternative lengthening of telomeres was reported in up to 30%, and possibly 50% of human tumors of different types. It is taught that L1RT is key factor in cancers of telomerase negative cells (page 9). Applicants teach that some cell lines are telomerase positive and some are telomerase negative (page 30), and that L1RT cancers can be induced in animal models. They further explain how to assay for telomerase activity in existing tumors (page 19).

Although this information is clearly important for Applicants' invention, it does not enable one of skill in the art to clearly recognize which cancers are treatable by the claimed methods, i.e., which cancers are due to or induced by LINE-1 RT.

Applicants Arguments addressed:

Applicants argue that methods for identifying ALT-type cancer cells are known in the art and/or taught by the instant specification. For instance, Applicants state that telomerase negative tumors are those that do not express or have the endogenous telomerase and yet show lengthening of telomeres, also referred to herein as alternative lengthening of telomeres (ALT). The LIRT mediated telomere lengthening in cells can be characterized by the presence of long and heterogeneous telomeres relative to the telomere lengthening mediated by telomerase. One skilled in the art would know how to determine the presence of long and heterogeneous telomeres characteristic of ALT in cells by carrying out, for example, TRF assay.

Applicants refer to Bryan et al., 1997, *Nature Medicine*, 3:1271-1274, as evidence for the idea that ALT type tumors are readily identifiable.

The Examiner agrees with Applicants that ALT-type cells present in tumors can be identified. However, Applicants are reminded that the language of the instant claims requires more than that. The language requires that the tumor or cancer treated by the instant method be one that is "due to" (claims 10 and 39) or "induced by" (claim 39) cells showing ALT. Applicants have not described any such cancers; Applicants have described how to identify cancers and solid tumors comprising ALT-type cells, but Applicants have not described cancers whose genesis is due to or induced by ALT. Accordingly, Applicants have not demonstrated they were in possession of methods for treating such cancers.

Furthermore, a comprehensive list of cancers "characterized by" cancer cells showing ALT (claim 1) is not described in the instant application. The phrase "characterized by" is ambiguous in that it is unclear what is or is not encompassed by the claimed method. What

cancers are "characterized by" cancer cells showing ALT? What are the criteria defining cancers "characterized by" ALT? It is unclear.

Instead of specifically describing such cancers, Applicants point to art-recognized methods for detecting telomerase expression and the presence of long, heterogeneous telomeres, and that a combination of such features is indicative of ALT. Thus, it appears from Applicants' remarks that biochemical assays and analyses are necessary to determine whether or not a particular tumor comprises, and is "characterized by," cells showing ALT. That is, many different cancers may comprise ALT, but a definitive determination must be made by assaying the tumor. Thus, it appears that the claimed methods require more than simply treating or administering, but require assaying and identifying beforehand to characterize the tumor as one treatable by AZT, ddI, or d4T.

The Examiner notes that the prior art teaches that different tumors from many different tissues may comprise cells showing ALT (see Bryan et al. (1997) *Nature Medicine* 3:1271-4, Table 1, page 1271 and page 1272, 1st column). The prior art teaches that cancers are by nature heterogenous, and may comprise both telomerase positive and telomerase negative cells. Bryan et al. (1997) *Nature Medicine* 3:1271-4 (cited by Applicants in their remarks, page 13) teach that some telomerase positive tumors have abnormally long TRFs similar to those seen in ALT cells. They suggest that some of these tumors may be heterogeneous, with regions containing telomerase and other regions exhibiting ALT (page 1273, 1st column). They further suggest that telomerase and an alternative telomere lengthening mechanism may coexist in the same cells. Bryan et al. teach that one can be certain that ALT exists only when telomerase is absent.

In another report, Bryan et al. (1997) *Eur. J. Cancer* 33:767-773 teach that ALT does not correlate with the method of immortalisation of the cell line. There are examples of telomerase-negative cell lines among those immortalised with SV40, HPV, and chemical carcinogens, and in spontaneously immortalised cell lines (page 769). There is also no correlation between telomerase activity and cells of a particular cell type; there are both telomerase negative and positive fibroblast, epithelial, and mesothelial cell lines (page 769, 2nd column). Additionally, they teach that cells of the same type and from the same individual may also be either telomerase or ALT-positive (page 769).

Thus, while the prior art clearly teaches the involvement of ALT in cell immortality, the prior art also teaches that tumors are sometimes heterogenous, in that they may comprise both telomerase negative and positive cells.

Adequate written description does not exist in the instant application for all cancers "characterized by" cancer cells showing alternative lengthening of telomeres. Stating that it is will within the skill in the art to identify such cancers does not help to describe the cancers themselves, which are now encompassed by the instant methods. The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Moreover, the instant application does not enable one of skill to envision the set of cancers encompassed by the instant claims since the instant application does not describe the criteria used to classify a given cancer as one that is "characterized by," induced by, or mediated by cells showing ALT or by ALT itself.

Accordingly, Claims 1, 2, 4, 6-15, 39 and 40 remain rejected for failing to provide written description of methods for treating any and all cancers that are characterized by and that are due to alternative lengthening of telomeres induced or mediated by LINE-1 RT, because no such cancers have been identified with reasonable clarity such that the skilled artisan would recognize that Applicants were in possession of the claimed methods.

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Claims 39 and 40 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for preventing cancer in a person in need thereof, wherein the cancer is due to cells showing alternative lengthening of telomeres induced or mediated by LINE-1 RT, comprising administering to the person a therapeutically effective amount of a composition comprising one or more nucleoside analogs. More specifically, the method is drawn to the prevention of those cancers listed in claim 40.

MPEP §2164.08 states in part that "The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

A thorough search of the prior art did not identify any explicit teachings stating that cancer of any form is preventable via administration of nucleoside analogs, as now claimed in

claim 39. However, post-filing art indicates that the treatment of cancer is highly unpredictable. Cancer is recognized to be a multifactorial event, in which numerous alterations contribute to the emergence of the malignant cell (Bocchetta et al., 2004, *Oncogene* 23:6484-6491). Malignant tumor growth is a dynamic process in which it is difficult to identify a unique event that caused the process (Bocchetta et al.). Human tumors of any given histological type have great genetic diversity, as revealed by gene expression profiling, and in most types of cancer only a subset of patients will prove responsive to any given agent (Chabner et al., 2005, *Nature Reviews Cancer* 65-72).

In view of these teachings, use of the claimed invention to treat cancer, least of all to prevent cancer, is considered to be highly unpredictable.

A review of the instant application (specifically at pages 29–31) finds one working example directed to the use of nucleoside analogs to inhibit cell growth in cultured cell lines. However, it is unclear how these *in vitro* results can be extrapolated to the claimed method of prevention of cancer in a human being. No additional guidance is provided in the specification as to how to use nucleoside analogs to prevent cancer, other than general assertions such as, for example, nucleoside analogs can be used to block ALT cancer (page 9), and AZT may be used to inhibit L1RT activity, apparently responsible for ALT.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Applicants' Arguments:

Applicants argue that the specification provides sufficient teachings to enable one of skill in the art to practice the invention as claimed without undue experimentation. Applicants argue that *in vitro* assays and models are acceptable models for demonstrating prevention of cancer in animals and humans, and may be reasonably correlated with *in vivo* methods for preventing cancer. Applicants assert that the references relied upon by the Examiner do not establish that cancer prevention by telomere maintenance is unpredictable.

The Examiner respectfully disagrees. MPEP §2164.03 states in part that

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)."

"I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim."

Applicants' general assertions that nucleoside analogs such as AZT inhibit cell growth in immortalized cell lines *in vitro* in cell culture and therefore will prevent cancer in vivo in any animal including humans is not persuasive. There is no evidence either in the specification or the prior art to indicate that any compound, including any nucleoside analog, may administered as prophylaxis to prevent cancer in any animal, including a human being.

The Examiner agrees that Applicants have shown that AZT may be used to inhibit cancer cell growth *in vitro* (see Example 1, p.29-31). However, the working example does not correlate with the claimed invention (MPEP §2164.02). In the instant case, Applicants are seeking to claim a genus of methods for preventing cancer in a person, wherein the cancer is due cells showing ALT. Inhibiting the growth of a model, immortalized cell line in culture is not enabling disclosure of a method for preventing cancer in a human.

Moreover, as explained in the previous Action, the prior and post-filing art teaches that cancer is a multifactorial process having many underlying causes and arising from a number of different biochemical and molecular biological abnormalities. Additionally, Bryan et al. (1997) *Nature Medicine* 3:1271-1274, which Applicants cite in their remarks at page 13, clearly teaches that tumors may be heterogeneous by nature, with regions containing telomerase and other regions exhibiting ALT. They also teach that ALT and telomerase activity may coexist in the same cell (page 1273, 1st column, bottom). They teach, for example, that one can be certain ALT exists only when telomerase is absent (page 1273, 1st column, bottom). Bryan et al. also teach that ALT is much higher in *in vitro* immortalized cell lines than in tumor derived cell lines (page 1272). Thus, Bryan et al. teach that the overall behavior, genotype and phenotype of immortalized cell lines in culture do not always reflect the activity and behavior of tumor cells encountered *in vivo*.

Accordingly, the instant claims remain rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 6, 7, and 9 under 35 U.S.C. 102(b) as being anticipated by Rideout et al. (US Patent 5,683,990) is withdrawn in view of the amendments to the claims and in view of the prior art evidence teaching and suggesting that Kaposi's sarcoma is a cancer substantially comprised of telomerase-positive cells (see Chen et al. (2001) *Exp. Biol. Med.* 226:753-757).

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The rejection of Claims 16, 17, 21, 22-24, 29, 36–38 under 35 U.S.C. 102(a) as being anticipated by Gan et al. (2002) *FEBS Lett.* 527:10–14 is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 102/103

The rejection of Claims 10, 11, 13, 15-17, 21, 22, 24, 29, and 37-39 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rideout et al. is withdrawn for the reasons given above.

Claim Rejections - 35 USC § 103

Applicants' amendments to the claims overcome the rejections of record under this section.

However, Applicants' amendments necessitate the following new grounds of rejection under this section.

Claims 1, 2, 4, 6-17, 19, 21-29, and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (1997) *Cancer Res.* 57:2341-5 (cited in previous Action), Delap et al. (1991) *Proc. Annu. Meet. Am. Soc. Clin. Oncol.* 10:A295, Doroshow et al. (1994) *Proc. Annu. Meet. Am. Soc. Clin. Oncol.* 13:146, Gomez et al. (1998) *Biochemical Biophysical Res. Comm.* 246:107-110, Bryan et al. (1997) *Nature Medicine* 3:1271-1274, Bryan et al. (1997) *Eur. J. Cancer* 33:767-773, and Kuo et al. (1998) *Biochemical Biophysical Res. Comm.* 253:566-570.

The invention is directed to methods for treating cancers mediated by or due to alternative lengthening of telomeres, or ALT. The specification teaches that ALT is primarily driven by a LINE-1 encoded reverse transcriptase, which operates independently of telomerase, also a reverse transcriptase. The specification teaches that ALT is observed in cells that are telomerase negative, or, stated another way, that telomerase negative tumors are those that do not express or have endogenous telomerase and yet show lengthening of telomeres, which lengthening is characterized by long heterogeneous telomeres (specification page 6). The specification teaches that ALT was reported in up to 30% of human tumors of different types, tumor-derived cell lines and human cell lines and up to 50% in some subsets of tumors and immortalized immortalized in vitro (page 2). With regard to the claimed embodiment, the specification teaches that AZT can be used for the treatment of up to 30% of cancer cases (page 31).

At the outset, the Examiner notes that the instant claims are directed to encompass methods "comprising administering to the individual a therapeutically effective amount of a composition comprising...AZT," and to encompass methods "comprising administering to

...cells an effective amount of AZT," and to methods "comprising contacting the cell with...AZT." Thus, the claims include open, "comprising" language and are considered to encompass methods using AZT alone or in combination with other agents, wherein the agents are administered together with AZT in a single composition or in conjunction with AZT prior to or after the administration of AZT.

The prior art is replete with reports teaching, demonstrating, and suggesting the use of AZT, either alone or in conjunction with another agent, to treat cancers of different types.

For instance, Wagner et al. teach that AZT can be used to inhibit rat mammary carcinomas *in vivo*. Detailed dosage regimens and results are provided (pages 2341-4). Wagner et al. suggest (page 2341), based on their results, that AZT alone may have therapeutic potential as an anti-breast cancer chemotherapeutic agent.

Delap et al. describe a phase I study of AZT for treating various cancers in patients. It is taught that 11 patients suffering from breast, colorectal, ENT, lung, and sarcoma were treated with AZT, and that 3 patients notes improvement in their cancer-related symptoms, and that additional patients were being entered on the program.

Doroshow et al. describe a study using AZT in combination with cisplatin to treat cancer in 25 patients. Tumor types included lung, breast, ovary, and others. It is said that 7 patients responded with a stable disease profile.

The prior art teaches or the least suggests that both telomerase positive and telomerase negative cells are present in a number of cancers, and that it is difficult to categorize a given cancer as either wholly telomerase positive or negative at all stages and in all tissues of the affected patient.

For instance, Bryan et al., Nature Medicine, teach that alternative lengthening of telomeres is found in a variety of different tumors and tumor cell lines, including bladder carcinoma, fibrosarcoma cell lines, and breast carcinoma (See Table 1, page 1271). For instance, 29% of breast cancer speciimens assayed were telomerase negative (page 1271) and at least one of the specimens displayed long telomeres. Bryan et al. teach that other reports, too, are consistent with the presence of ALT in tumors. For example, Bryan et al. cite a report in which 2 out of 56 renal carcinomas were telomerase negative and had cell clones with greatly elongated TRFs (page 1272). Five out of 47 melanomas lacked telomerase activity. Also, a neuroblastoma had elongated TRFs. Thus, in this report, Bryan et al. teach that a minority of tumors from different tissues have ALT type cells.

In another report, Bryan et al. (1997) *Eur. J. Cancer* 33:767-773 teach that ALT does not correlate with the method of immortalisation of the cell line. There are examples of telomerase-negative cell lines among those immortalised with SV40, HPV, and chemical carcinogens, and in spontaneously immortalised cell lines (page 769). There is also no correlation between telomerase activity and cells of a particular cell type; there are both telomerase negative and positive fibroblast, epithelial, and mesothelial cell lines (page 769, 2nd column). Additionally, they teach that cells of the same type and from the same individual may also be either telomerase or ALT-positive (page 769).

Gomez et al. teach that AZT causes telomere shortening in cells in culture. Gomez et al. explicitly state that "AZT must be viewed as a telomerase inhibitor with potential anticancer properties" (page 109). Gomez et al. further teach that AZT has been reported to inhibit the

growth of cultured human breast cancer cells and rat mammary tumors and shortens the telomeres of mice exposed *in utero* (page 109).

Kuo et al. teach that L1 transcripts are present in a large number of solid tumors and tumor cell lines (page 566). Applicants acknowledge this teaching in their remarks, page 14.

It would have been obvious to one of skill at the time the invention was made to use AZT to treat breast cancer in individuals suffering from cancer, as taught by Wagner et al., Delap et al., and Doroshow et al. It would further have been obvious to one of skill that AZT is effective for blocking telomere lengthening and that AZT has anti-cancer properties. Bryan et al. teach that some breast cancer tumors display ALT and that ALT may contribute to the progression of some breast cancers as well as other cancers. Gomez et al. teach and suggest using AZT as a general agent to block telomere lengthening.

Therefore, absent evidence to the contrary, the treatment of breast cancer by administering AZT to individuals suffering from breast cancer would have been prima facie obvious at the time the invention was made. One would have been both well motivated and had a reasonable expectation of success given that the properties of AZT as an anti-breast cancer therapeutic were known and suggested in the prior art, and given it was known and taught that one of skill may use AZT to block telomere lengthening (see Gomez et al.). Wagner et al, Delap et al., and Doroshow et al. all show that AZT may be used, in some cases, to effectively treat breast cancer in some patients.

The fact that AZT inhibits telomerase as well as L1-encoded reverse trancriptase is not essential to this prima facie showing, since such properties are inherent to AZT and necessarily flow from the disclosed methods for treating breast cancer. Additionally, the prior art suggests

the existence of ALT in at least some breast cancer tumors (Bryan et al. Nature Medicine). Additionally, based on the combined teachings of Bryan et al., showing that many different cancers, including breast cancer, may comprise ALT type cells in addition to telomerase positive cells, and given that it is not possible to describe a cancer as ALT without first testing the tumor using biochemical methods, and given that L1 transcripts are present in many types of tumors, there is sufficient reason to believe that the disclosed methods of Wagner et al, Delap et al., and Doroshow et al. for treating breast or mammary cancer in individuals using AZT disclose a methods for treating a cancer characterized by or due to ALT, and methods for interfering with telomere lengthening in telomerase negative cells.

The Examiner submits that the burden is shifted to the Applicants to show that the breast cancers treated by Wagner et al, Delap et al., and Doroshow et al. do not necessarily or inherently possess the characteristics required by the instant claims.

In view of the combined teachings of these references, taken as whole, the instantly claimed invention as a whole would have been *prima facie* obvious at the time the invention was made.

Response to Applicants' Arguments

Applicants' arguments presented on 4/10/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
May 31, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635